

Amendments to the Specification:

Please delete the Table of Contents section beginning at page 1, line 4 through page 2, line 29 of the originally filed specification.

Kindly enter the following three new paragraphs after the first full paragraph at p. 24 of the originally filed specification (or correspondingly the second full paragraph on page 19 of the substitute specification):

In one embodiment, therefore, the human insulin precursor refers to a polypeptide consisting of the human B chain and the human A chain of human insulin connected by a chemically or enzymatically cleavable amino acid residue, or a chemically or enzymatically cleavable peptide moiety having at least two amino acid residues which moiety can be enzymatically cleaved from and without disruption of both the A-chain and the B-chain.

The connecting moiety is preferably a polypeptide. The polypeptide generally has at least 2 and preferably from about 2 to about 35 and most preferably from about 6 to about 35 amino acid residues. The moiety is joined to the A-chain at the N-terminal amino group of the A chain (i.e., the A-1 residue) and to the B-chain at the carboxyl terminus (i.e., the B-30 residue). Most preferably, the connecting moiety, when it is a peptide, is the natural connecting peptide of human proinsulin, the C polypeptide thereof.

Although it is preferred to use the natural connecting sequence, as indicated above, much shorter peptide sequences can be used for the connecting peptide. The only requirements are (1) that they be of sufficient length to permit proper disulfide bond formation between the A- and B-chains, and (2) that they be cleavable from the insulin precursor with accompanying insulin formation. A typical dipeptide which can be used is -Arg-Arg-. In addition, modifications of the foregoing dipeptide having the formula -Arg-X'-Arg- in which X' represents at least one amino acid residue can be readily employed. Highly preferred connecting peptides are -Arg-Arg-Lys-Arg- as well as longer chain peptides having the structure -Arg-Arg-X²-Lys-Arg- in which X² is at least one amino acid residue and preferably at least two amino acid residues. These latter, of course, include the natural connecting peptide.